10034981/blessing

(FILE 'HOME' ENTERED AT 23:11:01 ON 02 MAY 2003)

FILE 'REGISTRY' ENTERED AT 23:11:13 ON 02 MAY 2003

```
L1             0 S VALPRIOC ACID/CN
L2             0 S VALPRIOC ACID
L3             1 S VALPROIC ACID/CN
L4             0 S VALPROATE/CN
L5            19 S VALPROATE
```

FILE 'ADISCTI, ADISINSIGHT, ADISNEWS, BIOSIS, BIOTECHNO, CANCERLIT, CAPLUS, CEN, DGENE, DRUGB, DRUGLAUNCH, DRUGMONOG2, DRUGNL, DRUGU, EMBAL, EMBASE, ESBIOBASE, IFIPAT, IPA, JICST-EPLUS, KOSMET, LIFESCI, MEDICONF, MEDLINE, NAPRALERT, NLDB, NUTRACEUT, ...' ENTERED AT 23:13:05 ON 02 MAY 2003

```
L6         42833 S L3
L7         34061 S L5
L8           328 S ACUTE MIGRAINE HEADACHE
L9           233 S L8 (P) TREAT?
L10            5 S L9 AND L6
L11            7 S L9 AND L7
L12            3 DUP REM L11 (4 DUPLICATES REMOVED)
L13            4 DUP REM L10 (1 DUPLICATE REMOVED)
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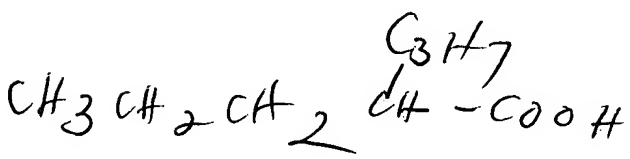
— applicants', date not good.
— applicants' date not good



Valproic acid

10034981/blessing

L13 ANSWER 1 OF 4 USPATFULL

ACCESSION NUMBER:	2002:280683 USPATFULL
TITLE:	Intravenous valproate for acute treatment of migraine headache
INVENTOR(S):	Edwards, Keith R., Williamstown, MA, UNITED STATES
PATENT ASSIGNEE(S):	LAHIVE & COCKFIELD, LLP. (U.S. corporation)

	NUMBER	KIND	DATE
PATENT INFORMATION:	US 2002156131	A1	20021024
APPLICATION INFO.:	US 2001-34981	A1	20011227 (10)

RELATED APPLN. INFO.: Continuation of Ser. No. US 2000-564521, filed on 4 May 2000, ABANDONED

	NUMBER	DATE
PRIORITY INFORMATION:	US 1999-132416P	19990504 (60)

DOCUMENT TYPE:	Utility
FILE SEGMENT:	APPLICATION
LEGAL REPRESENTATIVE:	LAHIVE & COCKFIELD, 28 STATE STREET, BOSTON, MA, 02109
NUMBER OF CLAIMS:	14
EXEMPLARY CLAIM:	1
LINE COUNT:	494

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention features a novel therapy for effecting acute **treatment** of migraine headache. The therapy involves intravenous administration of valproate and is equal to and in some respects superior to previously-known therapies for abortive **treatment** of prolonged moderate to severe **acute migraine headache**.

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L13 ANSWER 2 OF 4 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2002002568 EMBASE
TITLE: Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache.
AUTHOR: Edwards K.R.; Norton J.; Behnke M.
CORPORATE SOURCE: Dr. K.R. Edwards, Western New England Pain Center, Southwestern Vermont Medical Center, 140 Hospital Drive, Bennington, VT 05201, United States
SOURCE: Headache, (2001) 41/10 (976-980).
Refs: 18
ISSN: 0017-8748 CODEN: HEADAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

AB Objective - To determine the effectiveness and tolerability of intravenous valproate for the acute **treatment** of migraine headache with or without aura (International Headache Society diagnostic criteria 1.1 and 1.2) compared with intramuscular metoclopramide 10 mg followed 10 minutes later by intramuscular dihydroergotamine 1 mg. Background - Divalproex sodium is approved for prophylaxis of migraine headache. We studied the possible effectiveness of intravenous sodium valproate for the **treatment** of **acute migraine headache**. Valproate offers a **treatment** option for patients with migraine who recently have used a triptan or dihydroergotamine, theoretically avoiding the risk of drug interactions or cardiovascular complications. Design/Methods - In an open-label randomization, patients with an established diagnosis of migraine with or without aura were administered either intravenous valproate or intramuscular dihydroergotamine with metoclopramide to **treat** moderate-to-severe migraine headache of 24 to 96 hours' duration. Forty patients alternately received either 500 mg intravenous valproate or 10 mg metoclopramide intramuscularly followed by 1 mg dihydroergotamine. Patients rated severity of headache and the presence or absence of nausea, photophobia, or phonophobia at baseline, and at 1, 2, 4, and 24 hours. Results - With intravenous valproate, 50% of patients reported headache improvement from moderate or severe to none or mild at 1 hour following **treatment**, 60% reported such improvement at 2 hours, 60% at 4 hours, and 60% at 24 hours. Corresponding improvement rates for dihydroergotamine were 45% at 1 hour, 50% at 2 hours, 60% at 4 hours, and 90% at 24 hours. Intravenous valproate and intramuscular dihydroergotamine provided similar relief from associated migrainous symptoms (nausea, photophobia, and phonophobia) during the first 4 hours following **treatment**. While none of the patients who received intravenous valproate experienced drug-related side effects during **treatment**, 15% of patients who took dihydroergotamine experienced one or more episodes of nausea and diarrhea during the first 4 hours of **treatment**. Conclusions - Intravenous valproate is similar in effectiveness to dihydroergotamine/metoclopramide as abortive therapy for prolonged moderate-to-severe **acute migraine headache**. Although the results were not statistically significant (P=.3635), intravenous valproate appears to offer a safe, effective, and well-tolerated **treatment** for patients with acute migraine. Relative to dihydroergotamine/metoclopramide, however, headache relief was not as likely to be sustained at 24 hours as with intravenous valproate.

L13 ANSWER 2 OF 4 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
ACCESSION NUMBER: 2002002568 EMBASE
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AUTHOR: Edwards K.R.; Norton J.; Behnke M.
CORPORATE SOURCE: Dr. K.R. Edwards, Western New England Pain Center, Southwestern Vermont Medical Center, 140 Hospital Drive, Bennington, VT 05201, United States
SOURCE: Headache, (2001) 41/10 (976-980).
Refs: 18
ISSN: 0017-8748 CODEN: HEADAE
COUNTRY: United States
DOCUMENT TYPE: Journal; Article
FILE SEGMENT: 008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
LANGUAGE: English
SUMMARY LANGUAGE: English

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L13 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:790298 CAPLUS

L13 ANSWER 3 OF 4 CAPLUS COPYRIGHT 2003 ACS
ACCESSION NUMBER: 2000:790298 CAPLUS
DOCUMENT NUMBER: 133:329630
TITLE: Intravenous valproate for acute treatment of migraine headache
INVENTOR(S): Edwards, Keith R.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066109	A2	20001109	WO 2000-US12317	20000504
WO 2000066109	A3	20010215		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1181012	A2	20020227	EP 2000-928865	20000504
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002156131	A1	20021024	US 2001-34981	20011227

PRIORITY APPLN. INFO.: US 1999-132416P P 19990504
US 2000-564521 B1 20000504
WO 2000-US12317 W 20000504

AB The present invention features a novel therapy for effecting acute **treatment** of migraine headache. The therapy involves i.v. administration of valproate and is equal to and in some respects superior to previously-known therapies for abortive **treatment** of prolonged moderate to severe **acute migraine headache**.

L13 ANSWER 4 OF 4 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
ACCESSION NUMBER: 1999:410347 BIOSIS
DOCUMENT NUMBER: PREV199900410347
TITLE: Intravenous valproate for abortive **treatment** of **acute migraine headache**. Is there an anti-convulsant mechanism.
AUTHOR(S): Edwards, K. (1); Behnke, M. (1); Santarcangelo, V. (1)
CORPORATE SOURCE: (1) Neurological Research Center, Bennington, VT USA
SOURCE: Epilepsia, (1999) Vol. 40, No. SUPPL. 2, pp. 36.
Meeting Info.: 23rd International Epilepsy Congress Prague, Czech Republic September 12-17, 1999
ISSN: 0013-9580.
DOCUMENT TYPE: Conference
LANGUAGE: English

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DOCUMENT NUMBER: 133:329630
TITLE: Intravenous valproate for acute treatment of migraine headache
INVENTOR(S): Edwards, Keith R.
PATENT ASSIGNEE(S): USA
SOURCE: PCT Int. Appl., 17 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2000066109	A2	20001109	WO 2000-US12317	20000504
WO 2000066109	A3	20010215		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
RW: GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
EP 1181012	A2	20020227	EP 2000-928865	20000504
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO				
US 2002156131	A1	20021024	US 2001-34981	20011227

PRIORITY APPLN. INFO.:
US 1999-132416P P 19990504
US 2000-564521 B1 20000504
WO 2000-US12317 W 20000504

AB The present invention features a novel therapy for effecting acute **treatment** of migraine headache. The therapy involves i.v. administration of valproate and is equal to and in some respects superior to previously-known therapies for abortive **treatment** of prolonged moderate to severe **acute migraine headache**.

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L12 ANSWER 1 OF 3 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 1
AN 2002002568 EMBASE
TI Comparison of intravenous valproate versus intramuscular dihydroergotamine and metoclopramide for acute treatment of migraine headache.
AU Edwards K.R.; Norton J.; Behnke M.
CS Dr. K.R. Edwards, Western New England Pain Center, Southwestern Vermont Medical Center, 140 Hospital Drive, Bennington, VT 05201, United States
SO Headache, (2001) 41/10 (976-980).
Refs: 18
ISSN: 0017-8748 CODEN: HEADAE
CY United States
DT Journal; Article
FS 008 Neurology and Neurosurgery
037 Drug Literature Index
038 Adverse Reactions Titles
LA English
SL English
AB Objective - To determine the effectiveness and tolerability of intravenous valproate for the acute **treatment** of migraine headache with or without aura (International Headache Society diagnostic criteria 1.1 and 1.2) compared with intramuscular metoclopramide 10 mg followed 10 minutes later by intramuscular dihydroergotamine 1 mg. Background - Divalproex sodium is approved for prophylaxis of migraine headache. We studied the possible effectiveness of intravenous sodium valproate for the **treatment** of **acute migraine headache**. Valproate offers a **treatment** option for patients with migraine who recently have used a triptan or dihydroergotamine, theoretically avoiding the risk of drug interactions or cardiovascular complications. Design/Methods - In an open-label randomization, patients with an established diagnosis of migraine with or without aura were administered either intravenous valproate or intramuscular dihydroergotamine with metoclopramide to **treat** moderate-to-severe migraine headache of 24 to 96 hours' duration. Forty patients alternately received either 500 mg intravenous valproate or 10 mg metoclopramide intramuscularly followed by 1 mg dihydroergotamine. Patients rated severity of headache and the presence or absence of nausea, photophobia, or phonophobia at baseline, and at 1, 2, 4, and 24 hours. Results - With intravenous valproate, 50% of patients reported headache improvement from moderate or severe to none or mild at 1 hour following **treatment**, 60% reported such improvement at 2 hours, 60% at 4 hours, and 60% at 24 hours. Corresponding improvement rates for dihydroergotamine were 45% at 1 hour, 50% at 2 hours, 60% at 4 hours, and 90% at 24 hours. Intravenous valproate and intramuscular dihydroergotamine provided similar relief from associated migrainous symptoms (nausea, photophobia, and phonophobia) during the first 4 hours following **treatment**. While none of the patients who received intravenous valproate experienced drug-related side effects during **treatment**, 15% of patients who took dihydroergotamine experienced one or more episodes of nausea and diarrhea during the first 4 hours of **treatment**. Conclusions - Intravenous valproate is similar in effectiveness to dihydroergotamine/metoclopramide as abortive therapy for prolonged moderate-to-severe **acute migraine headache**. Although the results were not statistically significant (P=.3635), intravenous valproate appears to offer a safe, effective, and well-tolerated **treatment** for patients with acute migraine. Relative to dihydroergotamine/metoclopramide, however, headache relief was not as likely to be sustained at 24 hours as with intravenous valproate.
CT Medical Descriptors:
*migraine: DT, drug therapy
*headache: DT, drug therapy
drug efficacy
drug tolerability

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disease severity
treatment outcome
nausea: SI, side effect
photophobia
drug induced disease: SI, side effect
diarrhea: SI, side effect
drug safety
human
male
female
clinical article
clinical trial
randomized controlled trial
controlled study
adolescent
aged
adult
article
priority journal
Drug Descriptors:
*valproic acid: AE, adverse drug reaction
*valproic acid: CT, clinical trial
*valproic acid: CM, drug comparison
*valproic acid: DT, drug therapy
*valproic acid: IV, intravenous drug administration
*dihydroergotamine: AE, adverse drug reaction
*dihydroergotamine: CT, clinical trial
*dihydroergotamine: CM, drug comparison
*dihydroergotamine: DT, drug therapy
*dihydroergotamine: IM, intramuscular drug administration
*metoclopramide: AE, adverse drug reaction
*metoclopramide: CT, clinical trial
*metoclopramide: CM, drug comparison
*metoclopramide: DT, drug therapy
*metoclopramide: IM, intramuscular drug administration
RN (valproic acid) **1069-66-5**, 99-66-1; (dihydroergotamine) 511-12-6; (metoclopramide) 12707-59-4, 2576-84-3, 364-62-5, 7232-21-5

10034981/blessing

L12 ANSWER 3 OF 3 SCISEARCH COPYRIGHT 2003 THOMSON ISI
AN 1999:698900 SCISEARCH
GA The Genuine Article (R) Number: 225BU
TI Intravenous **valproate** for abortive **treatment** of **acute migraine headache**. Is there an anti-convulsant mechanism?
AU Edwards K (Reprint); Behnke M; Santarcangelo V
CS NEUROL RES CTR, BENNINGTON, VT
CYA USA
SO EPILEPSIA, (10 SEP 1999) Vol. 40, Supp. [2], pp. 36-36.
Publisher: LIPPINCOTT WILLIAMS & WILKINS, 227 EAST WASHINGTON SQ, PHILADELPHIA, PA 19106.
ISSN: 0013-9580.
DT Conference; Journal
FS LIFE
LA English
REC Reference Count: 0
CC CLINICAL NEUROLOGY

10034981/blessing

L12 ANSWER 2 OF 3 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.DUPLICATE 2
AN 1999:410347 BIOSIS
DN PREV199900410347
TI Intravenous valproate for abortive **treatment** of **acute migraine headache**. Is there an anti-convulsant mechanism.
AU Edwards, K. (1); Behnke, M. (1); Santarcangelo, V. (1)
CS (1) Neurological Research Center, Bennington, VT USA
SO Epilepsia, (1999) Vol. 40, No. SUPPL. 2, pp. 36.
Meeting Info.: 23rd International Epilepsy Congress Prague, Czech Republic September 12-17, 1999
ISSN: 0013-9580.
DT Conference
LA English
CC Pharmacology - General *22002
Biochemical Studies - General *10060
Pathology, General and Miscellaneous - Diagnostic *12504
Pathology, General and Miscellaneous - Therapy *12512
Sense Organs, Associated Structures and Functions - General; Methods *20001
Nervous System - General; Methods *20501
Cardiovascular System - General; Methods *14501
General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals *00520
BC Hominidae 86215
IT Major Concepts
Neurology (Human Medicine, Medical Sciences); Pharmacology
IT Diseases
acute migraine headache: abortive **treatment**, diagnosis, vascular disease, nervous system disease; phonophobia: ear disease; photophobia: eye disease
IT Chemicals & Biochemicals
dihydroergotamine: antimigraine - drug, intramuscular; metoclopramide: antimigraine - drug, intramuscular; sodium valproate: anticonvulsant mechanism, antimigraine - drug, intravenous
IT Miscellaneous Descriptors
Meeting Abstract; Meeting Poster
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae): patient
ORGN Organism Superterms
Animals; Chordates; Humans; Mammals; Primates; Vertebrates
RN 99-66-1 (VALPROATE)
1069-66-5 (SODIUM VALPROATE)
511-12-6 (DIHYDROERGOTAMINE)
364-62-5 (METOCLOPRAMIDE)